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Strategic alliances and market risk

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Strategic alliances in product development and marketing are crucial to the biotechnology industry. Many alliances, however, are terminated before the drug reaches the market. In this article we make the case that strategic alliances can fail because of how they are negotiated. Alliance contracts are often inflexible and do not allow for changes in market conditions. We propose a model for contract valuation that can assist biotech and/or pharma deal makers in negotiating alliances that have a higher chance of survival in uncertain market conditions. The model makes use of variable royalties and milestone payments. Because licensing is key to the biotech and/or pharma business model this article will be of interest not only to professionals in licensing, but to all professionals active in the industry.

Biotechnology (biotech) companies focused on the development of new compounds operate in a market that is characterised by regulatory, technical and market risk. Moreover, the development requires large amounts of financial resources. The high failure rate of biotech start-ups, in addition to the increasingly complex regulatory environment and the lack of exit opportunities through public offerings, has therefore left the financial community wary of investment. According to a recent survey published in October 2011 by the US National Venture Capital Association (http://www.nvca.org), 39% of 150 venture capital (VC) firms interviewed has decreased its investment in life sciences during the past 3 years and the same proportion expect to continue to do so over the next three years. Numerous VC firms, including 3i, Excalibur and Prospect, have pulled out from investing in biotech altogether. The VC funds that do invest in biotech have investment horizons too short to finance R&D projects all the way from discovery to market. In the current environment biotech companies rely heavily on VC funding and are therefore unable to raise sufficient capital to develop drugs all the way to market.

Owing to their focus on the early stages of drug development biotech companies rarely see direct sales revenues from their projects. Therefore they must be creative and seek returns elsewhere. For this reason many biotech companies have adopted a business model that hands over development of their assets to pharmaceutical companies (pharma) in the form of strategic alliances. Biotech and/or pharma alliances typically generate revenues from a milestone and royalty (M&R) based model. These alliance contracts include upfront down payments upon signing, milestone payments associated with achieving defined targets in the development process, and royalties as a percentage of sales. Biotech companies, by out-licensing projects at an early stage, are thus able to secure revenue with which to sustain and build their company. Strategic alliances have become essential for developing drugs to market and today an important revenue stream for early stage and small biotech companies comes from licensing deals with pharma [1].

According to Recap Deloitte, during the period 1977–2010 as many as 71% of all product alliances were terminated before the drug reached the market, with only 33% of alliances terminated because of a lack of efficacy or safety. In addition, Recap Deloitte reports that out of all product alliances that have been terminated 55% are still pursued by the licensor [You're Fired! A Quantitative Analysis of Dissolved Deals: http://www.bioworld.com/content/youre-fired-quantitative-analysis-dissolved-deals-0]. This suggests that on top of the expected technical hurdles, a significant portion of alliances are terminated for strategic or economic reasons. Termination is expensive because it causes lost opportunity cost and damages public perception of the quality of the drug or company. The cost of termination is reflected in the drop in stock price that is often witnessed at the side of the licensor once an alliance is terminated. One example of this is the termination of Celltech's tumour necrosis factor (TNF)-inhibitor

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monoclonal antibody (mAb) Cimzia. When Pfizer returned its rights in November 2003 after failing to renegotiate, Celltech's shares plunged as much as 27%. Cimzia, however, is now marketed for the treatment of Crohn's disease. Another example is Exelixis' anticancer drug cabozantinib, which was partnered to Bristol-Myers Squibb (BMS). When BMS decided to terminate the alliance in June 2010, Exelixis' stock dropped by 16% on the day of announcement. Development of cabozantinib is now being continued by Exelixis for several oncology indications.

In this article we make the case that alliances can fail because of the ways and procedures under which the agreements are negotiated and the negotiation strategy employed. As a result, many alliance contracts do not react to changes in market conditions. Furthermore, the approaches used to determine market valuation of a contract, as described in the literature, fail to incorporate market risk [2]. We propose a simple framework for contract valuation that enables deal makers to negotiate alliances that are more resilient to changes in market conditions. This model is based on variable royalties and flexible milestone payments and is illustrated using a hypothetical R&D project.

Current practice

The most widely used methods for determining deal structures is benchmarking and discounted cash flow (DCF) analysis. Benchmarking provides a straight forward method to determine the potential value of a deal, because it gives an indication of what the market is prepared to pay for comparable deals. The caveat of its use, however, is that benchmarks are based on historical data and that changes in the market might make it out of date. In addition, the available data are likely to be biased owing to the selective reporting of deal terms which might cause benchmarks to be skewed towards the better deals.

By contrast, DCF analysis provides more fundamental insight in the value of a particular deal. One common approach to value alliances from the perspective of the biotech company is to estimate the peak sales of the drug, then outlay all the costs, milestones and royalty payments coming from the alliance and finally to discount these cash flows by the appropriate risk-adjusted cost of capital. This could be summarized in the following equation:

$$\mathrm{NPV} = \sum_{i=0}^{n}\left(\frac{P_i \times R_i}{e^{r\times i}}\right) - \sum_{i=0}^{n}\left(\frac{P_i \times C_i}{e^{r\times i}}\right) \qquad (1)$$

where NPV is the risk adjusted net present value of undertaking the alliance, P is the probability of incurring revenue R or cost C in year i, and r is the discount rate.

Taking this approach, however, does not determine the total size of the opportunity and also does not specify the division of total profits among the two parties. It is therefore worthwhile performing a similar exercise for the other party, or both parties combined, to see how much is being rewarded relative to the contribution.

One significant drawback to using DCF models for negotiating deal terms is the fact that these models are static and do not deal with potential changes in market conditions. DCF models are built on point estimates, such as expected peak sales and the NPV therefore indicates the average expected outcome or the 'most likely' scenario. The model, however, does not give insight into the probability of that outcome occurring. It would be necessary to perform a Monte Carlo simulation to reveal the probabilities of that and other outcomes. In practice products more often than not do not pass clinical trials. If they do reach the market then the chances are that the peak sales estimated at the outset are no longer up-to-date. Throughout a decade of development, changes in economic conditions or clinical profile of the drug can change the sales outlook of the drug drastically. For the alliance this means that the financial terms on which the alliance was built no longer satisfy.

To illustrate this we take a hypothetical Phase I project 'mAb-1', owned by Biotech A that will be licensed to Pharma B. Let us assume that both parties agree on the most likely scenario of US$ 800M peak sales and a corresponding NPV of 200 M (see the supplementary material online). Let us also assume that after long hours of negotiating, A and B have agreed to the M&R payment scheme shown in Table 1. The M&R scheme comes down to a 1:4 (20–80%) division of value in favour for pharma[1].

As the sensitivity analysis of Fig. 1 shows, however, the 1:4 division is only realised when peaks sales is exactly as projected. The figure

TABLE 1

M&R payment scheme as agreed between biotech A and pharma B

M&R payment scheme	$ M
Upfront	5
Phase II	10
Phase III	10
BLA filing	15
Launch	25
Royalty rate	5.0%
Total NPV biotech A	40

Abbreviations: BLA: Biological License Application; M&R: Milestones & royalties; NPV: Net present value.

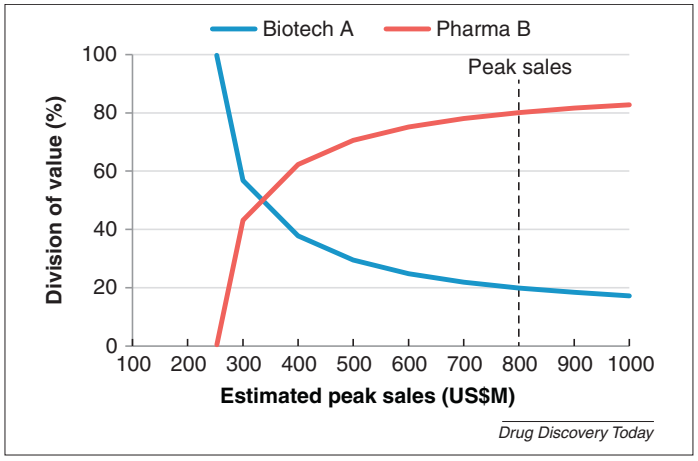

FIGURE 1

Sensitivity analysis. Shows the sensitivity analysis of NPV for both Biotech A and Pharma B (*y*-axis) versus estimated peak sales (*x*-axis). The 1:4 division is only realised when peak sales turn out exactly US$ 800M. Pharma B will abandon the project once the peak sales estimate falls below US$ 228M. Derived using Excel 2010 Data Table (see the supplementary material online). Abbreviation: NPV: Net present value.

[1] For phase I projects the division of value will be often between 1:4 and 1:5 in favour for pharma.

also reveals that Pharma B will terminate the partnership once peak sales projections fall below $228M. At this point the combination of development costs and M&R payments will be higher than projected sales causing the NPV to fall below zero. This shows that although high milestones are seemingly attractive to the licensor, they are in fact hazardous to the partnership in 'down scenarios', because they are fixed and take away flexibility.

These findings suggest that changes in the economic environment or clinical profile of the drug could lead to termination of perfectly viable drugs that could benefit patients. The financial terms of the deal therefore have a significant part in the economic success to both parties and hence to the success of the partnership. This article seeks to identify a framework for contract valuation in the biotech and/or pharma industry that can be used to determine the financial terms of the deal and takes into account market uncertainty.

The framework

We propose the use of a model for contract valuation that deals with uncertain market conditions. Using this framework both parties will negotiate the division of value based on the relative contribution of each party. The zone of potential agreement in negotiations is the range in which both parties are better off than they would be without the deal. In this line of thinking, the NPV of the intellectual property might be seen as such a zone of potential agreement. Finance theory dictates that any project with an NPV that is positive is worthwhile undertaking, because this would yield a higher than required rate of return. Conversely, no party would accept contractual terms that would reduce this value to less than zero. The negotiation process should therefore be focused to find the sweet-spot in which the NPV of the project is divided according to the relative contribution of each party [3]. The deal terms should then include a mechanism that protects this division of value.

Valuation models are typically not shared during negotiations. As a result each party has the natural tendency to overestimate its own contribution to the partnership and underestimate that of its future partner. As the previous section suggests, this might well result in driving a hard bargain for milestones which might increase the risk of termination. It is therefore of importance to understand what will make the project worthwhile for the potential alliance partner. The formation of an alliance is not a single transaction, but results in an ongoing partnership that should be built on shared expectations. Moreover, monetary gain from the alliance is not a zero sum game but is dependent on the effort both partners put into the partnership. It is therefore recommended that both partners develop a joint model to be used during the negotiating process.

TABLE 2

The variable royalty tiers and the respective NPV values for biotech A and pharma B. Royalties and NPVs were derived using Excel 2010 Goal Seek (see the supplementary material online)

Sales	Royalties (%)	NPV A (US$)	NPV B (US$)
0	0	5	(50)
100	0	5	(20)
200	0	8	8
300	0	10	37
400	2	15	62
500	3	22	86
600	4	28	111
700	5	34	136
800	5	40	160
900	5	46	185
1000	6	52	209

As the example, mAb-1 shows standard M&R contracts do not mitigate changes in market conditions. For this reason it is recommended to incorporate one or more elements of financial flexibility to the contract. We use a combination of variable royalties and flexible milestones to achieve this. Other possibilities include sales milestones, indication driven milestones and caps and ceilings on royalties. These methods could be equally valid, but are not further discussed in this article. Variable royalties are an established approach to help address uncertainty in peak sales [The Royalty Rate Report 2010: A Comprehensive Assessment of Valuation in the Pharmaceutical Sector. 2010: www.pharmaventures.com]. In current practice, however, they primarily deal with upside. As we will show in the next paragraph, royalty tiers can be tailored to deal with both 'up' and 'down' scenarios. By contrast, flexible milestones are not widely practiced. With flexible milestones partners re-evaluate the market of the product when each milestone is reached to determine the size of the payment. One approach to this could be using a specific market forecast model that is agreed upon by both parties. In some circumstances it might be necessary to include the changes in development costs.

Let us have another look at our hypothetical monoclonal mAb-1. Table 2 shows the value that each party will receive using variable royalties. Between estimated peak sales of US$ 400M and US$ 1B the division of risk and reward is stable. As Fig. 2 indicates, the project is worth execution in a larger range of scenarios than when fixed

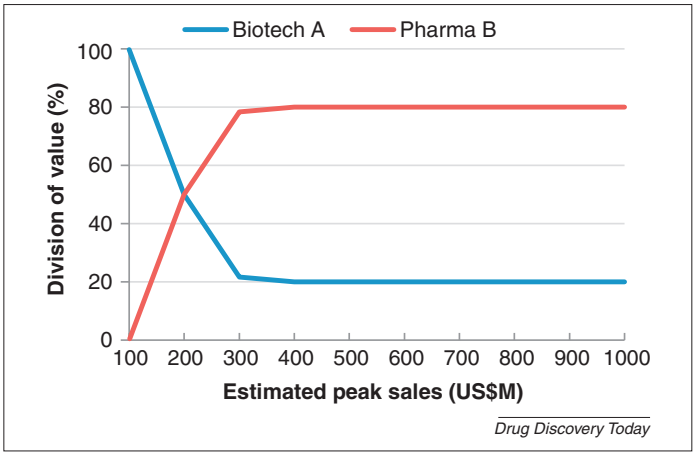

FIGURE 2

Sensitivity analysis. Shows the division value for each party (*y*-axis) versus estimated peak sales (*x*-axis) if variable royalties are used. As this figure shows, the 1:4 division is maintained between peak sales US$ 400M–US$ 1000M. Pharma will abandon the project only once the peak sales estimate falls below US$ 173M.

royalties and milestones would have been used. Only if the market size falls below US$ 173M will the pharma company decide to abandon the project for economic reasons.

Concluding remarks

In this article a simple valuation framework is proposed that deals with market uncertainty and that will enable biotech and/or pharma deal makers to negotiate alliances that have a higher chance of survival in uncertain market conditions. Variable royalties and flexible milestones can be used to share the downside and the upside from fluctuations in market outlook. By using this approach alliances will retain a pre-agreed division of value and as such keep the alliance healthy. This is relevant because it will increase the probability of viable, non-blockbuster status drugs, reaching patients.

One reservation biotech companies could have for applying this model is that they would have to bear a larger portion of market risk. Biotech companies might wish to reduce risk by maximising milestone payments. This article shows, however, that fixed milestone payments increase the risk of termination of the partnership. These should be avoided because the costs of termination are high as in many cases commercially viable products have been dropped. Furthermore, after alliance termination the drug company might be perceived as having made incorrect decisions in the market place. In other words, an increase in the probability of the drug reaching the market should be able to offset market risk. In addition, negotiating a deal that shares risk also enables the transaction to take place. This increases the probability to be able to work with the partner of choice, which enhances the image of the biotech company. This could be used to secure future deals or further venture funding.

Deal makers might not be willing to share financial models during the negotiating process. They might be anxious that this compromises their negotiating position. Deal makers should bear in mind, however, that alliances do not comprise a single transaction, but are ongoing partnerships that should be built on shared expectations. It is therefore important that the expectations and motivations are aligned throughout the partnership. For that reason, it is recommended that deal makers should enter negotiations not with the aim to maximise own gain but to maximise the value of the partnership. Deal makers might also argue that value is different to both parties because of differences in assumptions, such as the perception of attrition rates. Negotiating assumptions, however, is useful because this gives insight into the perception of the value and risk of the project by the other side.

It can be shown that the approach outlined in this article is a useful addition to the existing practices in alliance valuation. Because licensing is key to the biotech and/or pharma business model, the proposed model will be of interest not only to professionals in licensing, but to all active in the industry.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.drudis.2012.03.008.

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